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09/980,039	08/06/2002	Bonnie Davis	U 013729-7	8014

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LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

EXAMINER	
MITCHELL, GREGORY W	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,039	DAVIS, BONNIE	
	Examiner	Art Unit	
	Gregory W Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 11-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the remarks filed on October 12, 2004. Claims 1-22 are pending. Claims 23 and 24 have been cancelled. Claims 4-10 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-3 and 11-22 are examined herein.

The rejections of the previous Office Action are hereby withdrawn. The following rejections now apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific acetylcholinesterase inhibitors, as claimed in claims 11-22, does not reasonably provide enablement for any compound capable of inhibiting acetylcholinesterase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The recitation, "acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours," is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention

is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method of treating conditions that can benefit from the stimulation of the hypothalamic-pituitary-gonad axis by the administration of an acetylcholinesterase inhibitor.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a treatment comprising the administration *any* acetylcholinesterase inhibitor with a central effect and a duration of action of from 1 to 100 hours. The nature of the invention is complex in that it potentially encompasses any compound capable of such an effect.

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of acetylcholinesterase inhibitors that would be useful in a method of the instant invention is limited. Applicant discloses galantamine, lycoramine, donepezil and rivastigmine, and analogues thereof, as acetylcholinesterase inhibitors useful in the instant invention. The specification does not teach that the scope of the invention is limited to these acetylcholinesterase inhibitors, however.

It is further noted that the claims attempt to further limit the scope of the claims by the function of the compound as opposed to the structure of the compound. Claim 2 is drawn to an acetylcholinesterase inhibitor that has a duration from 1.5 to 72 hours. While these claims may actually limit the types of compounds that may be used in the instant invention, one of ordinary skill in the art would not be apprised of how these limitations limited the scope of the structure of the compounds useful therein. Therefore, not only would one of ordinary skill in the art not be apprised of the scope of the generic invention, but would not be apprised of the limitations of the dependant claims even if the if the metes and bounds of the independent claim 1 were well defined.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter

sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus ..." at 1406 (empahasis added).

In the instant case, "acetylcholinesterase inhibitor," recited in the instant claims is purely a functional distinction. Hence, these functional recitations read on any compounds that might have recited functions. However, the specification merely provides a limited number of examples of compounds for the various kinds of functional compounds possible.

Thus, Applicant's functional language at the points of novelty fail to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted." *General Electric Co. v. Wabash Appliance Corp.* 37 USPQ at 468 (US 1938).

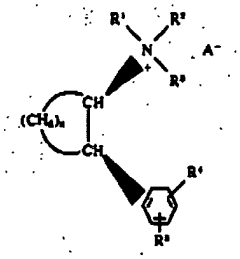
(4). ***Working Examples***:

No working example of treating the failure of ovulation is disclosed. On pages 7-8, Applicant merely recites instructions on a mode of administering galantamine or rivastigmine for inducing ovulation.

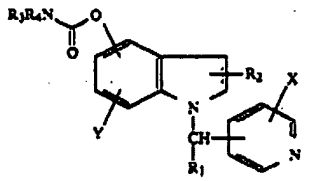
(5). ***State of the Art***:

Acetylcholinesterase inhibitors are known to have a variety of markedly different structures.

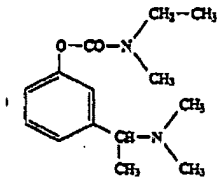
For example, Lewis et al. (USPN 3998843) teaches compounds of the following formula as acetylcholinesterase inhibitors:



Effland et al. (USPN 5264442) teaches compounds of the following formula as acetylcholinesterase inhibitors :



Enz (USPN 5602176) teaches compounds of the following formula as acetylcholinesterase inhibitors:



Accordingly, the state of the art is such that there is no common structural feature which connects acetylcholinesterase inhibitors, one to another, nor would one of

ordinary skill in the art be apprised of the scope of the invention as herein claimed.

(6). ***Predictability of the Art***:

The invention is directed to acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours in general, wherein the structure of those compounds is limited only by the function of the compounds. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compounds represented by an "peripheral opioid antagonist," which may encompass countless compounds. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page

51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any compound represented by "acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours." As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

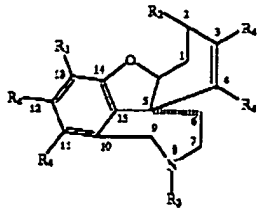
Claims 1-3 and 11-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Walles et al. (*European Journal of Obsterics and Gynecology and Reproductive Biology*, 4 (1S), s103-s107) in view of each of Yorke et al. (*Biology of Reproduction*, 22(4), 897-912), Trubnikova et al. (*Ontogenez*, 20(5), 532-542, relying on English abstract), and Davis et al. (USPN 6150354).

Walles et al. teaches that acetylcholine causes contraction in human and cow follicles (p s107). Walles does not specifically teach the administration of an acetylcholinesterase inhibitor or that contraction of follicles induces ovulation.

Yorke et al. teaches that muscular contraction is associated with the expulsion of the egg from the follicle in vertebrates.

Trubnikova et al. teaches that contraction of follicular epithelium cells resulted in the retraction of the egg envelopes.

Davis et al. teaches that acetylcholinesterase inhibitors of the following formula:



wherein R1 may be a monoalkyl or dialkyl carbamate, etc. It is also noted that galanthamine, and specific alkyl carbamates are taught as acetyl cholinesterase inhibitors (col. 29, line 35-col.30, line 60). Davis et al. also teaches that it is possible to increase acetylcholine levels by decreasing the amount or activity of the acetylcholinesterase (col. 7, lines 44-48).

It would have been obvious to one of ordinary skill in the art to administer an acetylcholinesterase inhibitor of Davis et al. in order to induce ovulation because (1) Davis et al. teaches that the inhibition of acetylcholinesterase causes an increase in acetylcholine; (2) Walles et al. teaches that acetylcholine causes the the follicles to contract; and (3) both Yorke et al. and Trubnikova teach that the contraction of follciles is associated with the release of the egg (ovulation). One would have been motivated to administer the acetylcholinesterase inhibitors of Davis et al. because of an expectation of success in inducing release of the egg from the follicle.

It is noted that the claimed recitation of a central effect and a duration of action of from 1 to 100 hours is a property of the acetylcholinesterase to be administered. Since the same compounds are cited herein as obvious, the limitation is met. A compound and its properties are inseperable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

It is further noted that the combined references have rendered obvious a treatment for the induction of ovulation. Accordingly, the combined references render obvious a treatment of a condition which can benefit from the stimulation of the hypothalamic-pituitary-gonad axis (failure to ovulate).

Claim Rejections - 35 USC § 103

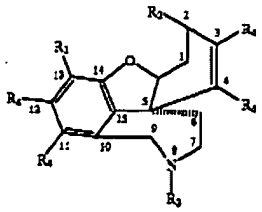
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 11-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Saiko et al. (82CA:96010) in view of Davis et al. (USPN 6150354).

Saiko et al. teaches that augmented cholinergic processes stimulate the release of the egg from the follicle.

Davis et al. teaches that acetylcholinesterase inhibitors of the following formula:



wherein R1 may be a monoalkyl or dialkyl carbamate, etc. It is also noted that galanthamine, and specific alkyl carbamates are taught as acetyl cholinesterase inhibitors (col. 29, line 35-col.30, line 60). Davis et al. also teaches that it is possible to

inhibitors (col. 29, line 35-col.30, line 60). Davis et al. also teaches that it is possible to increase acetylcholine levels by decreasing the amount or activity of the acetylcholinesterase (col. 7, lines 44-48).

It would have been obvious to one of ordinary skill in the art to administer an acetylcholinesterase inhibitor of Davis et al. in order to induce ovulation because (1) Davis et al. teaches that the inhibition of acetylcholinesterase causes an increase in acetylcholine; and (2) Saiko et al. teaches that cholinergic activity stimuates the release of the egg from the follicle (ovulation). One would have been motivated to administer the acetylcholinesterase inhibitors of Davis et al. because of an expectation of success in inducing release of the egg from the follicle (inducing ovulation).

It is noted that the claimed recitation of a central effect and a duration of action of from 1 to 100 hours is a property of the acetylcholinesterase to be administered. Since the same compounds are cited herein as obvious, the limitation is met. A compound and its properties are inseperable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

It is further noted that the combined references have rendered obvious a treatment for the induction of ovulation. Accordingly, the combined references render obvious a treatment of a condition which can benefit from the stimulation of the hypothalamic-pituitary-gonad axis (failure to ovulate).

Response to Arguments

Applicant's arguments with respect to claims 1-3 and 11-22 have been considered but are moot in view of the new ground(s) of rejection. The arguments are addressed below as they apply to the instant rejections.

Applicant's arguments that acetylcholinesterase inhibitors with the instantly claimed functional limitations are enabled is not persuasive because functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406. See the instant 35 USC 112(1) rejection above.

Applicant argues, "[t]he present invention is essentially directed to use of acetylcholinesterase inhibitors to stimulate the HPG axis by influencing the secretion of gonadotropin releasing hormone" and "such treatments typically require administration of the specified compounds for several weeks at least." These arguments are not persuasive. It is pointed out that Applicant is arguing limitations that are not in the claims. There is no limitation in the claims that the treatment of the disorder associated with the HPG axis be treated by the stimulation thereof, simply that the it is a disorder that may be so treated. It is also noted that there is no limitation in the claims as to the duration of treatment required.

Applicant argues that "[r]abbits, but not humans, are reflex ovulators." This argument is not persuasive because there is no limitation in the claims as to the type of species involved in the treatment.

Applicant argues that Yorke et al.; Trubnikova, and Saiko et al. are not pertinent because the "references showing the extrusion of the egg could be promoted by acetylcholine do not address the two to three weeks before ovulation when the follicle is growing an egg large enough for ovulation." Again, these arguments are not persuasive because these limitations are not in the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER